

International Implantable Pump Study

Diabetes Clinical Trial Research 2007: Where we are, where do we go from here?













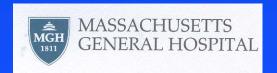


















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Controlled Clinical Trials

Controlled clinical trials are prospective human experiments that examine in a scientifically rigorous and ethically acceptable way the effect(s) of intervention(s).

Effects (outcomes) may include: safety, efficacy (symptoms, lab outcomes, morbidity and mortality), quality-of-life.



Controlled Clinical Trials

Controlled clinical trials have become *de facto* the most important means of establishing new interventions and, in the case of medications, the only route to approval



Ontogeny of Multicenter Clinical Trials

- Epidemiology- generates associations
 - Physiology- generates mechanisms, probes may become medications
 - Small scale experiments/trials

Multicenter clinical trials

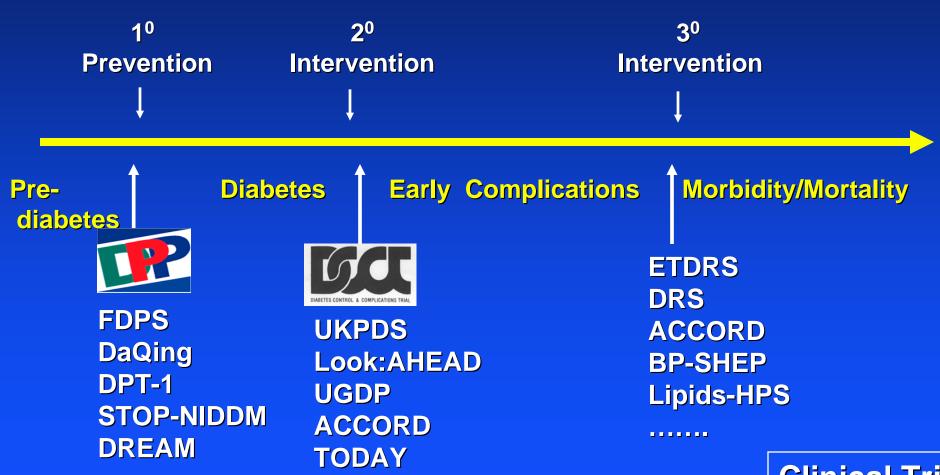
Large investment must be justifed based on generally consistent/convincing preliminary data

Ontogeny of Multicenter Clinical Trials

Do clinical trials only provide obvious answers?

- No
- Only clinical trials can provide a quantitative measure of effects of intervention(s)
 - Benefits
 - Risks
- Facilitate an estimate of risk to benefit
- Assess tolerability/acceptance
- Economic analysis

Controlled Clinical Trials in Diabetes



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Clinical Trials

What We Have Accomplished

What We Know-2007

- Type 2 diabetes (plague form) can be prevented
 - Intensive therapy- lower glycemic exposure over time- results in improved outcome
 - -Results in Type 1 diabetes most persuasive
 - Most effective when implemented early
 - -Appears to apply to all complications in type 1
 - Microvascular
 - Neuropathic
 - Cardiovascular

What We Have Accomplished

What We Know-2007

- Progression to more advanced complications including severe morbidity/mortality can be reduced
 - Blindness: laser, vitrectomy
 - Renal disease: BP (ACE-I, ARB), dialysis, transplantation
 - Amputation- foot care (less well established)
 - CVD- glycemia (type 1), BP, lipids, bypass (stent), aspirin

Clinical Trials

Limitations

They do not usually:

- Compare all available therapeutic options
- Establish the most cost-effective interventions
- Determine the translation potential of interventions in the community ("second translational block")
 - Patient/community acceptance
 - Large scale, cost-effective means of introducing/maintaining therapy

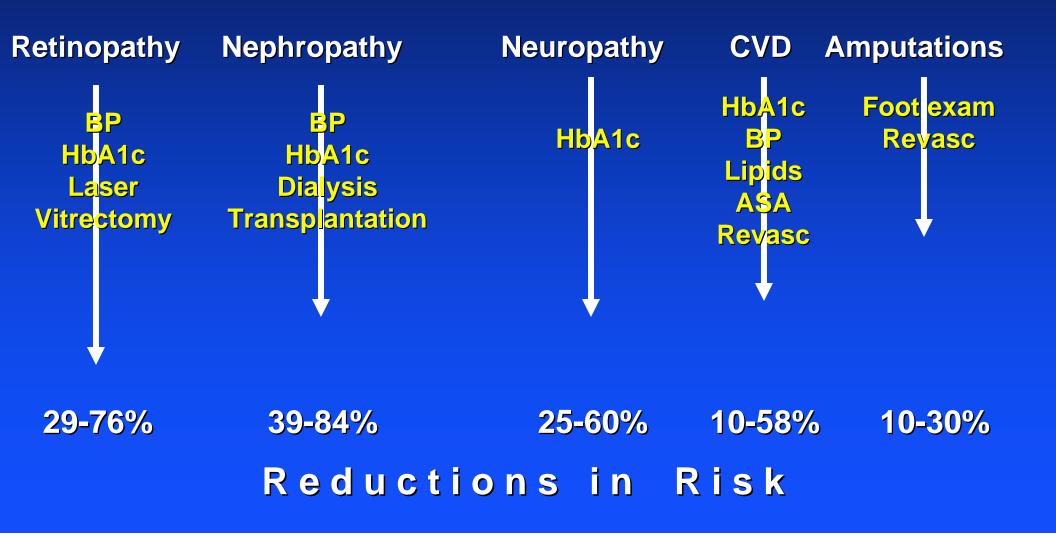
Clinical Trials

Limitations

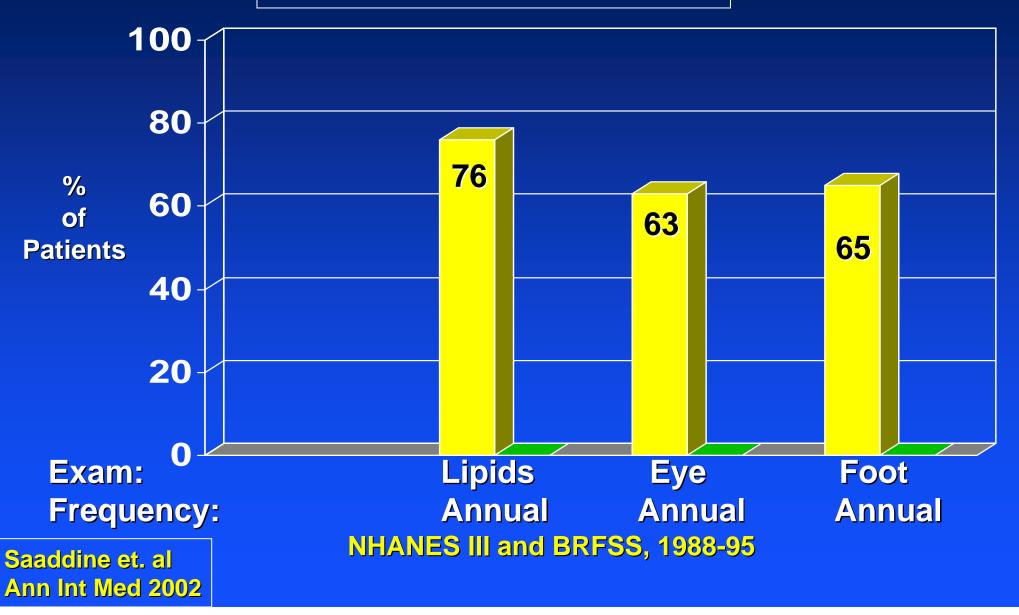
By virtue of their experimental nature, clinical trials usually establish principles of therapy.

Prevention/Treatment of Diabetes and its Complications

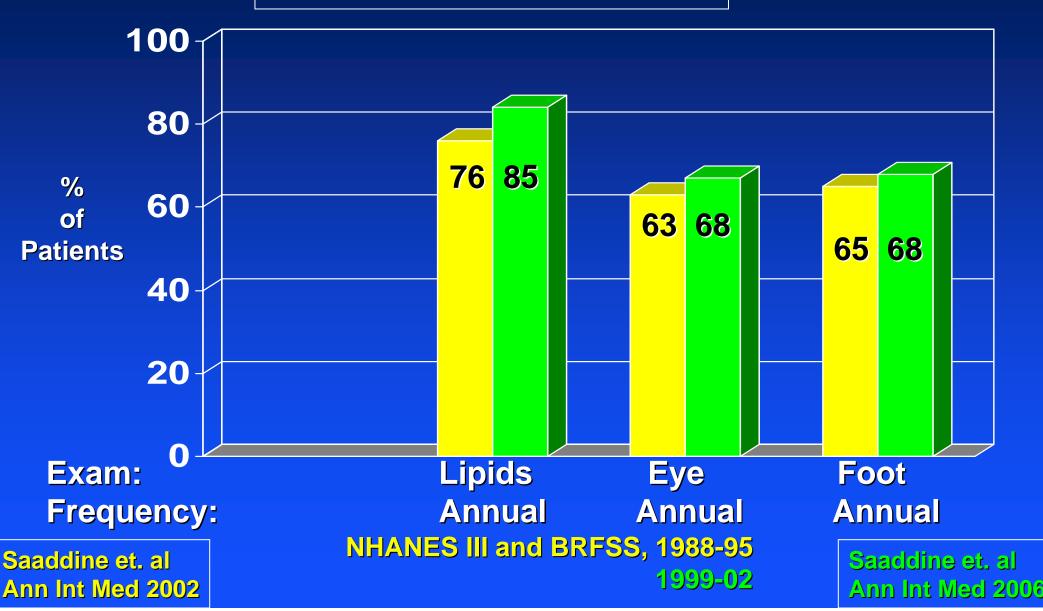
Evidence-based Medicine



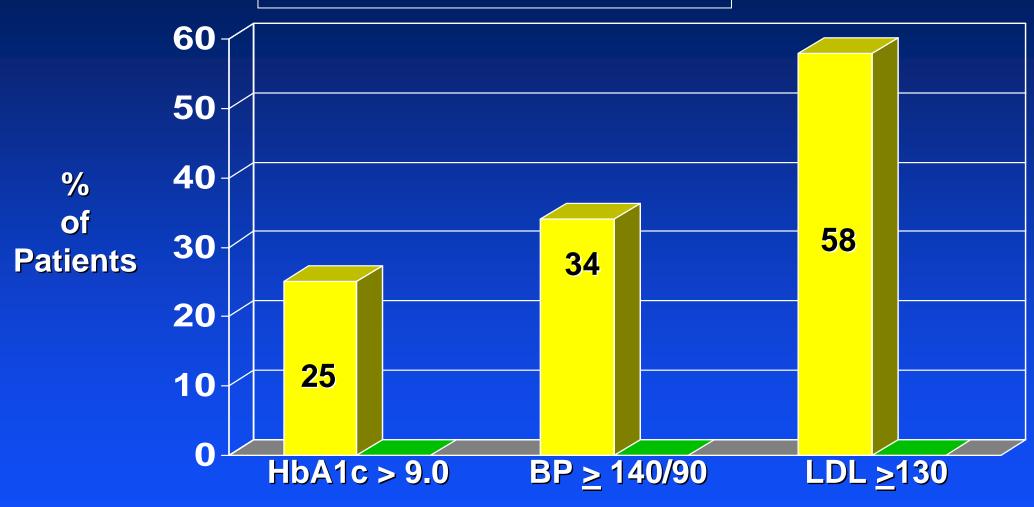
Adherence to DQIP Indicators



Adherence to DQIP Indicators



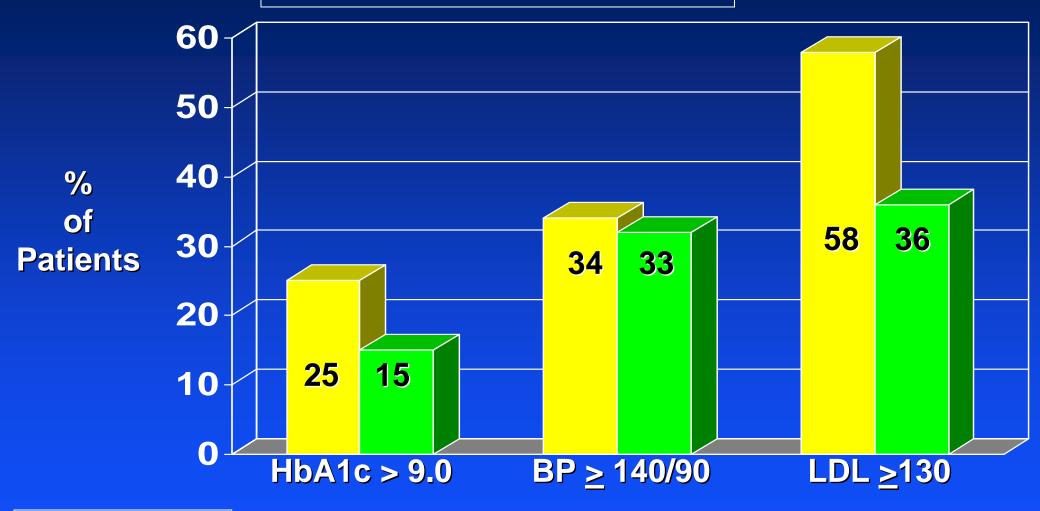
Adherence to DQIP Indicators



Saaddine et. al Ann Int Med 2002

NHANES III and BRFSS, 1988-95

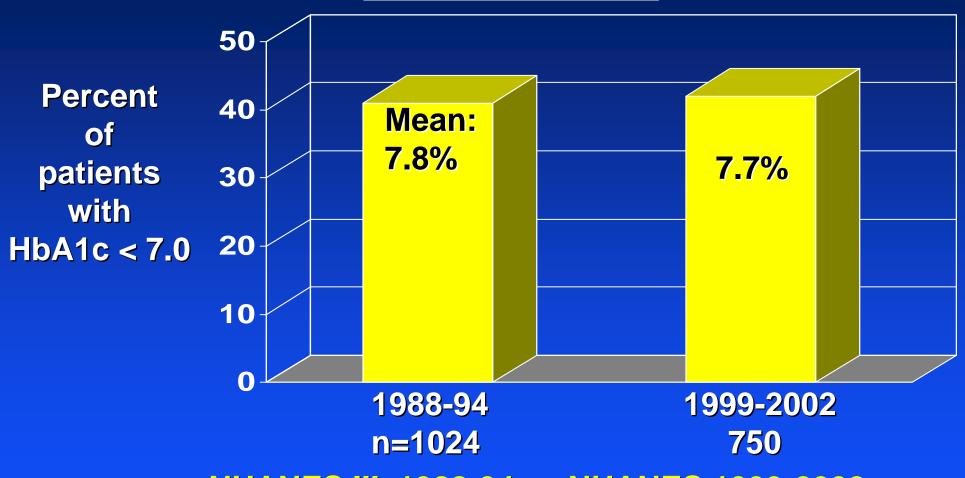




Saaddine et. al Ann Int Med 2002 NHANES III and BRFSS, 1988-95 1999-02

Saaddine et. al Ann Int Med 2006

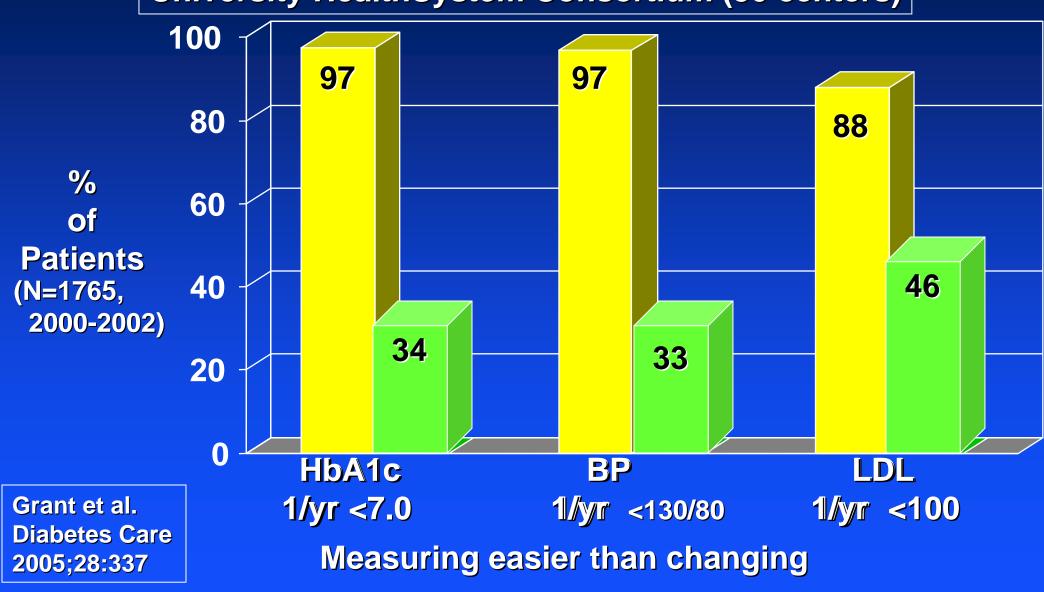
Recent Progress?



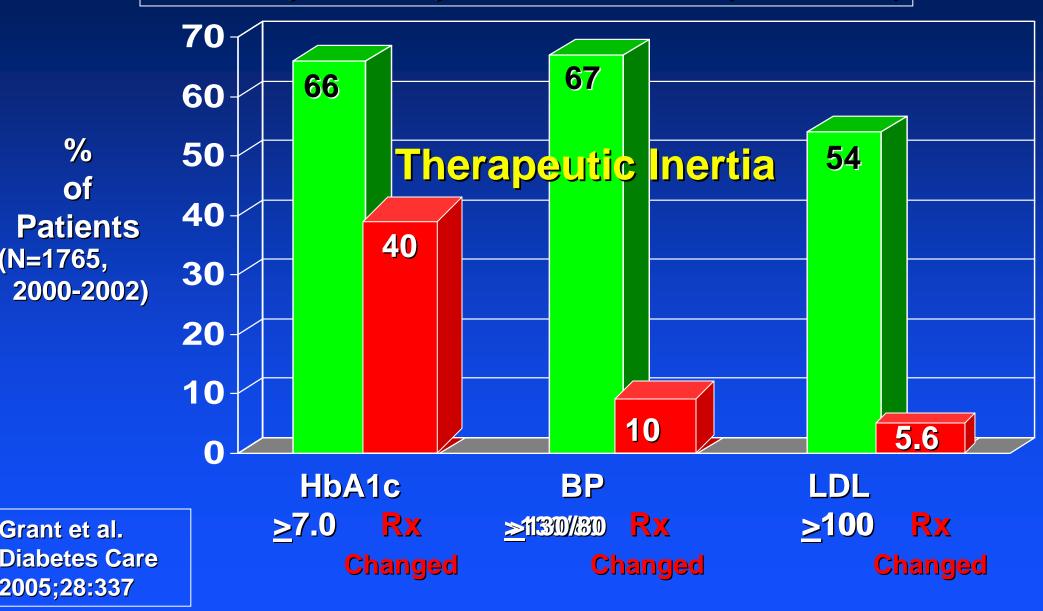
NHANES III, 1988-94 vs NHANES 1999-2002

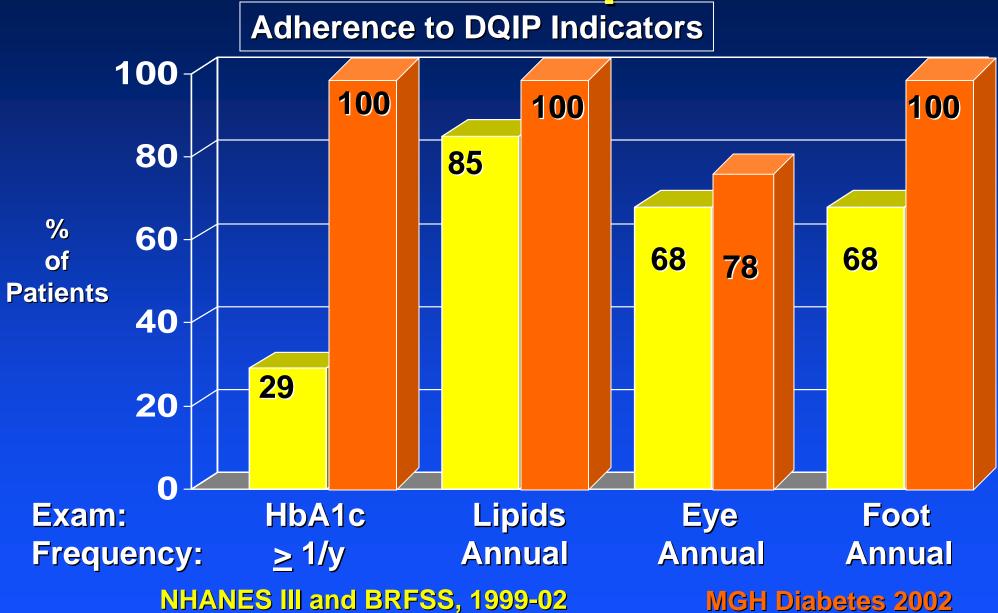
Saaddine et. al Ann Int Med 2006

University HealthSystem Consortium (30 centers)

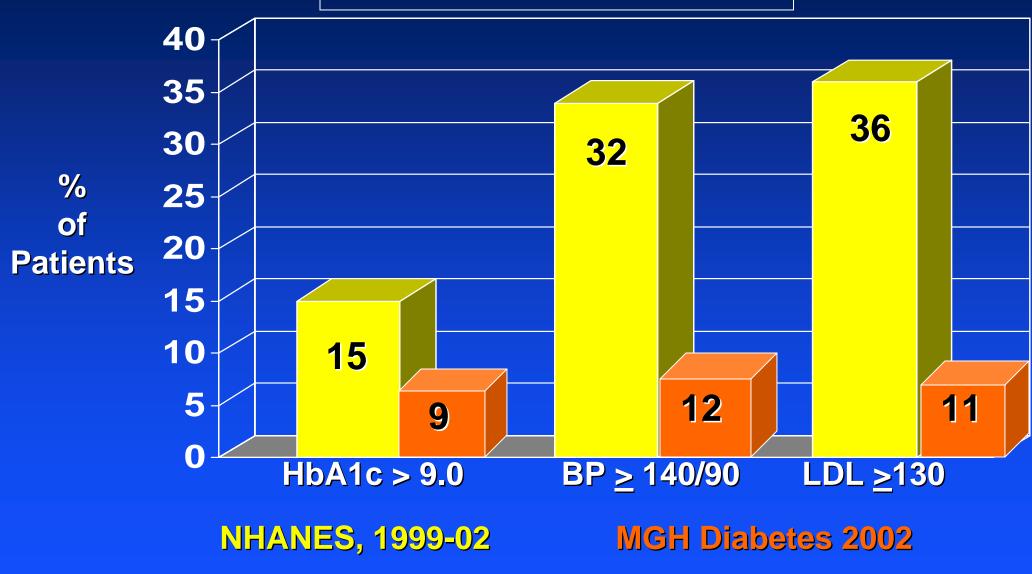


University HealthSystem Consortium (30 centers)





Adherence to DQIP Indicators



What We Have Accomplished What We Don't Know

Management

- Best (widely applicable, specific populations, costeffective) means of achieving normoglycemia
 - Type 1 diabetes
 - Type 2 diabetes
- Role of intensive therapy in the elderly
- Inpatient diabetes care
 - Level of control
 - -Subsets

What We Have Accomplished

What We Don't Know

Prevention

- Best means of prevention
- Prevention vs early intervention
- How to implement clinical trial results most effectively (and cost-effectively) in community

The Next Step

Advantages

- We have established surrogates for prevention and amelioration of disease/preservation of long-term health
- Don't necessarily need to incorporate hard endpoints (mortality, severe morbidity) that require very large scale, long-term expensive trials (especially if goal is not to establish principle of therapy for FDA)
 - -HbA1c
 - Microalbuminuria
 - Blood pressure
 - Lipids
 - Other CVD

The Next Step

Advantages

- Highly experienced clinical trial centers established
- Much experience in conducting clinical trials
- Common disease and large population at risk
 - For diabetes development
 - For complications
- High profile disease and condition
 - Major public health implications
 - Major economic implications
 - Political demand for studies that address public health and chronic diseases
- Highly motivated patient population

The Next Step

Disadvantages

- Little experience in designing/conducting studies that examine translation
- Little interest by industry in performing balanced comparison studies- low likelihood of support
- Although clinical science community is convinced of merits of experimental methods, designing valid, high yield experiments at the community level is potentially problematic
 - Real life interventions
 - Wide-spread application of interventions with potential dilution of effectiveness
 - Real life populations- effectiveness vs efficacy
 Like reality tv- messy

Goal(s) of Next Major NIDDK Trial(s)

- Positive impact on public health
- Build on current knowledge base
 - Expand and refine knowledge regarding currently effective interventions
 - Improve translation/application of current interventions
 - Maximize benefits
 - Target applications
 - Minimize cost
- ~5 year study- "moderate" funding available

Today's Goals

- Discuss and come to a general consensus on 4-6 potential projects in the areas of management and prevention
 - After more detailed presentations of unanswered questions in management and prevention of type 2, management of type 1, and management of the elderly
 - Review a compiled list of projects in plenary session
 - Supplement list with any topics that fulfill criteria
 - Poll participants to gauge relative enthusiasm for specific topics

Today's Goals

- The most "popular" potential project areas (probably 3-4) will be given to each of the two working groups, management and prevention
- During 3 hours after lunch, the projects will be discussed in detail by the working groups with the goal of preparing initial outline proposals for 2-3 studies from Management and 2 from Prevention for the Institute to consider
- Reconvene in plenary session for the studies to be presented and discussed (~ 1 hour)